PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/425 | A1

(11) International Publication Number: WO 97/46238

(43) International Publication Date: 11 December 1997 (11.12.97)

(21) International Application Number: PCT/GB97/01521

(22) International Filing Date: 6 June 1997 (06.06.97)

(30) Priority Data:
9611947.4 7 June 1996 (07.06.96) GB

(71) Applicant *(for all designated States except US)*: GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

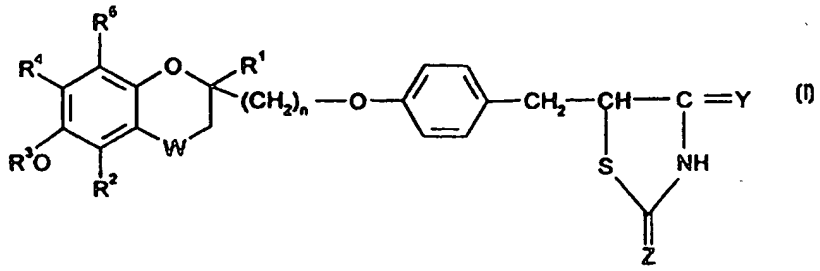
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: COMINACINI, Luciano [IT/IT]; Instituto di Semeiotica e Nefrologia Medica, Ospedale Policlinico, I-37134 Verona (IT).

(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MEDICAMENTS FOR AMELIORATING ENDOTHELIAL CELL ACTIVATION



(I)

(57) Abstract

The use of a compound of formula (I) in which: R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group; R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, a (C_5 - C_7 cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C_1 - C_6 alkoxy) carbonyl group or a benzoyloxycarbonyl group; R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylenedioxy group; n is 1, 2 or 3; W represents the $-CH_2$, > CO or > CH-OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may by the same as or different from R^3); and Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.

FOR THE PURPOSES OF INFORMATION ONLY

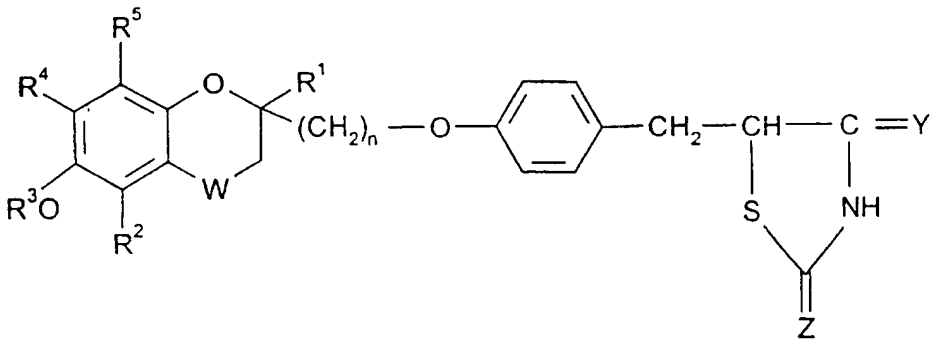
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

MEDICAMENTS FOR AMELIORATING ENDOTHELIAL CELL ACTIVATION

The present invention relates to the use of thiazolidine derivatives for ameliorating endothelial cell activation.

European patent no. 0139421 describes thiazolidine derivatives of formula (I):



in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, a (C_5 - C_7 cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C_1 - C_6 alkoxy) carbonyl group or a benzoyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the -CH-, >CO or >CH-OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

and pharmaceutically acceptable salts thereof.

The compounds are said to show blood lipid metabolism ameliorating activity and to have the ability to decrease the levels of blood lipid peroxides, blood triglycerides and blood cholesterol.

International patent application publication no. WO94/19347 describes the ability of compounds of formula (I) to inhibit the oxidation and/or peroxidation of low density lipoprotein (LDL) and suggests that the compounds may therefore have utility in the treatment of arteriosclerosis.

We have now surprisingly found that compounds of formula (I) reduce the activation of endothelial cells and are therefore useful in the treatment of disorders associated with endothelial cell activation.

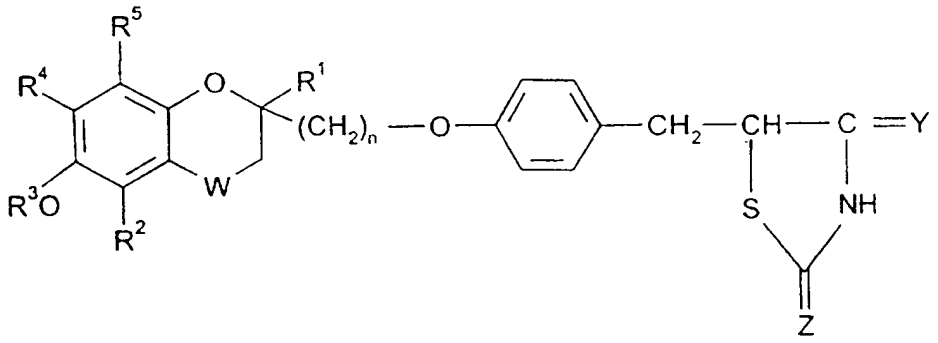
The vascular endothelium maintains a non-thrombogenic surface on the inside of blood vessels, regulates the growth and differentiation of underlying tissues and plays a pivotal role in controlling trafficking of leukocytes in inflammatory conditions. Perturbations in endothelial functioning are implicated in many diseases, including atherosclerotic and inflammatory diseases.

Activation of the endothelial cell in post-capillary venules leads to increased expression of adhesion molecules and consequent recruitment of blood leukocytes into adventitial tissue. Whilst this is a necessary step in the physiological defence mechanisms to foreign bodies, inappropriate endothelial cell activation is implicated in pathological inflammatory states.

The activation state of endothelial cells is at least in part determined by the effect of so-called inflammatory mediators, such as TNFα, interleukin-1. These agents are secreted by inflammatory cells, and cause activation of endothelial cells. A typical response of endothelial cells to such activation is to increase expression of adhesion molecules on the cell surface which allows recruitment of blood leukocytes to sites of inflammation. Therefore the level of adhesion molecules on the surface of endothelial cells can be taken as a measure of activation of the cells under inflammatory stimulus.

Such endothelial cell activation is also thought to be the initiating event for atherosclerotic cardiovascular disease. These arterial plaques contain macrophages and lymphocytes recruited from plasma by adhesion molecules on the endothelial cell surface. The macrophages in particular have been implicated in the acute symptoms (such as angina pectoris, myocardial infarction) associated with atherosclerotic plaques.

In a first aspect, the present invention provides the use of a compound of formula (I):



in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, a (C_5 - C_7 cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or

naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C_1 - C_6 alkoxy) carbonyl group or a benzoyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2$, >CO or >CH-OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.

In a second or alternative aspect, the invention provides a method for the treatment of an animal, including man, suffering from inappropriate endothelial cell activation, which method comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

As will be appreciated by those skilled in the art, references herein to treatment extend to prophylaxis as well as to the treatment of established disorders or symptons thereof.

In a preferred aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a

a medicament for the amelioration of endothelial cell activiation in atherosclerotic cardiovascular disease, including angina, myocardial infarction, peripheral vascular disease and cerebrovascular disease.

The invention further provides a method for the amelioration of endothelial cell activation in an animal, including man, suffering from atherosclerotic cardiovascular disease, including angina, myocardial infarction, peripheral vascular disease and cerebrovascular disease which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further preferred aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an inflammatory disorder associated with inappropriate endothelial cell activation.

The invention further provides a method for the treatment of an animal, including man, suffering from an inflammatory disorder associated with inappropriate endothelial cell activation, which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Inflammatory disorders associated with inappropriate endothelial cell activation include, for example, rheumatoid arthritis; systemic lupus erythamatosis; renal diseases including glomerulonephritis; hypertension and complications thereof; tissue reperfusion damage; adult respiratory distress syndrome; radiation-induced injuries; burns; inflammation in asthma, influenza and chronic bronchitis; inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease, non-steroidal anti-inflammatory drug induced damage and inflammatory and secretory effects of bacterial infection, e.g. due to *Clostridium difficile*; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge (i.e. urinary) incontinence; eye and dental inflammation, e.g.

gingivitis and periodontitis; and neurodegenerative diseases such as Alzheimer's disease.

It will be appreciated by those skilled in the art that formula (I) is intended to include all stereoisomers, including enantiomers and diastereoisomers, and mixtures thereof including racemates.

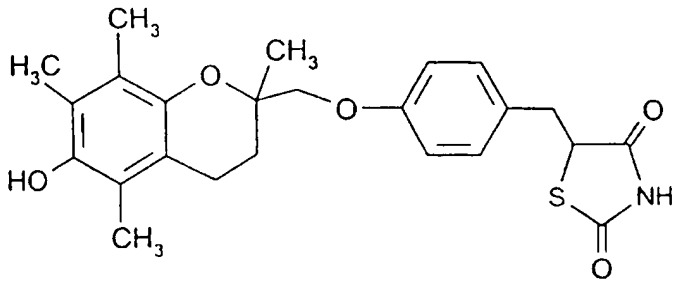
In compounds of formula (I) it is preferred that:

R^1 represents C_{1-4}alkyl;
R^2 represents H or C_{1-3}akyl;
R^3 represents H, C_{1-4}aliphatic acyl, unsubstituted C_{7-11} aromatic acyl or C_{2-4}alkoxycarbonyl;
R^4 represents C_{1-4}alkyl; and
R^5 represents H or C_{1-3}alkyl.
More preferably R^3 represents H, acetyl, benzoyl or ethoxycarbonyl.

Most preferably:

R^1 represents methyl;
R^2 represents H or methyl;
R^3 represents H, acetyl or ethoxycarbonyl;
R^4 represents methyl or t-butyl; and
R^5 represents H or methyl.

A particularly preferred compound for use in accordance with the present invention is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, represented by formula (IA):



(IA)

The compound of formula (IA) is also known as troglitazone.

Compounds of formula (I) and their pharmaceutically acceptable salts may be prepared as described in EP 0139421.

It will be appreciated that the amount of a compound of formula (I) required for use in treatment according to the invention will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patent and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.5 to about 20mg/kg of bodyweight per day preferably in the range of 0.1 to 15 mg/kg/day, most preferably in the range of 1 to 10mg/kg/day, such as about 50 - 500mg per day for a normal adult.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 800mg, conveniently 20 to 500mg, most conveniently 50 to 500mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

A pharmaceutical formulation will comprise a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and or/ prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. Oral and parenteral administration are preferred. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a pre-determined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary, or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintigrants or wetting agents. The tablets may be coated

according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and /or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by a aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the combinations according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as

gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other commonly used, materials in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, paste, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be carriers.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurised packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressure pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellent such as dichlorodifluoromethane, trichlorofluromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a value to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions for use in the present invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The inhibitory effect of the compound of formula (IA) on endothelial cell activation is demonstrated by the following Examples, which are illustrative of the present invention and not limitative thereof.

The invention is further illustrated by the following non-limitative example.

Example:

Endothelial cells from human umbilical veins (HUVECs) were isolated by conventional methods, maintained in culture and used between passages 2 and 4.

To aid solubility of troglitazone, human low density lipoprotein (isolated by serial density centrifugation) was used as a carrier. 5µg of troglitazone was incubated with LDL for 24h at 4°C in M-199 medium containing 10% foetal calf serum. Troglitazone containing LDL was purified by gel-filtration and any contaminating endotoxin removed by passing the troglitazone over a pre-packed endotoxin affinity column.

Troglitazone-containing LDL was incubated with HUVECs in M-199 medium at 37°C for 24h. After this time the troglitazone-containing medium was removed.

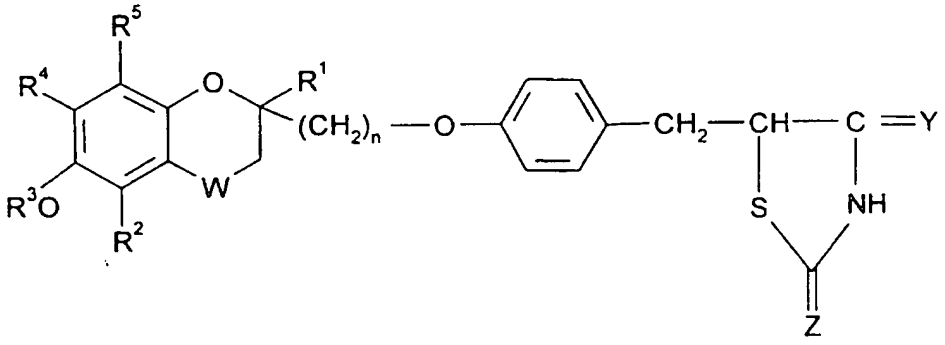
The HUVECs were incubated with TNFα (100U/ml, Sigma) in M-199 medium at 37°C for 24h. After this time, the level of VCAM-1 on the cell surface was measured using antibody detection in a FACS machine by conventional methods.

The results are presented in Figure 1.

The presence of troglitazone in the pre-incubation clearly attenuates the expression of the adhesion molecule VCAM-1 in response to the inflammatory mediator TNFα.

Claims

1. The use of a compound of formula (I):



in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1 - C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1 - C_6 aliphatic acyl group, a (C_5 - C_7 cycloalkane) carbonyl group, an aromatic acyl group which is a benzoyl or naphthoyl group optionally with one or more nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents, a heterocyclic acyl group having one or more oxygen, sulphur or nitrogen hetero atoms and with 4 to 7 ring atoms, an optionally halo-substituted phenylacetyl or phenylpropionyl group, a cinnamoyl group, a (C_1 - C_6 alkoxy) carbonyl group or a benzoyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1 - C_5 alkyl group or a C_1 - C_5 alkoxy group, or R^4 and R^5 together represent a C_1 - C_4 alkylenedioxy group;

n is 1, 2 or 3;

W represents the $-CH_2$, >CO or >CH-OR^6 group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the amelioration of inappropriate endothelial cell activation.

2. Use of a compound according to Claim 1 wherein;
R^1 represents C_{1-4} alkyl;
R^2 represents H or C_{1-3} alkyl;
R3 represents H, C_{1-4} aliphatic acyl, unsubstituted C_{7-11} aromatic acyl or C_{2-4} alkoxcarbonyl;
R^4 represents C_{1-4} alkyl
and
R^5 represents C_{1-3} alkyl
or a pharmaceutically acceptable salt thereof.

3. Use of a compound according to Claim 2 wherein R^3 represents H, acetyl, benzoyl or ethoxycarbony, or a pharmaceutically acceptable salt thereof.

4. Use of a compound according to claim 2 wherein;
R^1 represents methyl;
R^2 represents H or methyl;
R^3 represents H, acetyl or ethoxycarbonyl
R^4 represents methyl or t-butyl and
R^5 represents H or methyl,
or a pharmaceutically acceptable salt thereof.

5. Use according to claim 1 where the compound is troglitazone.

6. A method for the treatment of an animal, including man, suffering from inappropriate endothelial cell activation which method comprises administration or a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

7. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the amelioration of endothelial cell activation in atherosclerotic cardiovascular disease.

8. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of an inflammatory disorder associated with inappropriate endothelial cell activation.

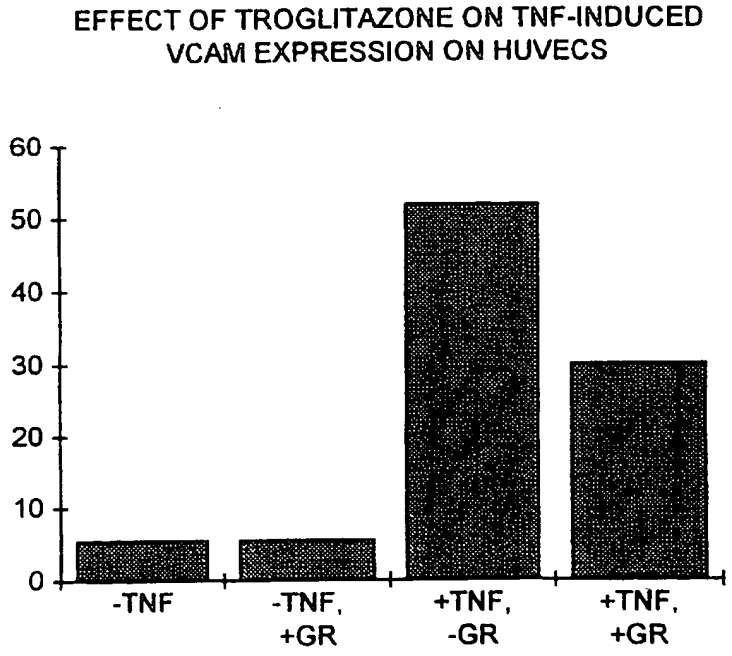

EFFECT OF TROGLITAZONE ON TNF-INDUCED
VCAM EXPRESSION ON HUVECS
60
50
40
30
20
10
0
-TNF
-TNF,
+GR
+TNF,
-GR
+TNF,
+GR

FIG. 1

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 97/01521

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LAW: "Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia" J. CLIN. INVEST., vol. 98, no. 8, 15 October 1996, pages 1897-1905, XP002042268 see the whole document ---	1-6
A	EP 0 139 421 A (SANKYO COMPANY LTD) 2 May 1985 cited in the application see whole document, especially pages 119-121 ---	1-7
A	WO 94 19347 A (SANKYO COMPANY LTD) 1 September 1994 cited in the application see abstract ---	1-7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 1997	17.10.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

:national Application No
PCT/GB 97/01521

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 07697 A (WARNER-LAMBERT COMPANY) 23 March 1995 see page 39, line 24 - line 36 see page 40, line 1 - line 12 ---	1-7
A	EP 0 319 288 A (PFIZER INC.) 7 June 1989 see page 2, line 16 - line 47 ---	1,7
A	EP 0 312 913 A (KORTH R.) 26 April 1989 see page 2, line 11 - line 18 ---	7,8
A	POBER: "Cytokine-mediated activattion of vascular endothelium" AM. J. PATHOL., vol. 133, no. 8, 1988, pages 426-433, XP002042269 see the whole document -----	8

1

INTERNATIONAL SEARCH REPORT

Iornational application No.
PCT/GB 97/01521

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 6
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No
PCT/GB 97/01521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 139421 A	02-05-85	JP 1604002 C	22-04-91
		JP 2031079 B	11-07-90
		JP 60051189 A	22-03-85
		AU 570067 B	03-03-88
		AU 3255984 A	07-03-85
		CA 1263395 A	28-11-89
		DE 3470742 A	01-06-88
		IE 58036 B	16-06-93
		MX 9203564 A	01-09-92
		US 4572912 A	25-02-86
WO 9419347 A	01-09-94	AU 6114794 A	14-09-94
		JP 7041423 A	10-02-95
WO 9507697 A	23-03-95	US 5457109 A	10-10-95
		AU 1770997 A	29-05-97
		AU 1771097 A	29-05-97
		AU 678291 B	22-05-97
		AU 7724994 A	03-04-95
		AU 679572 B	03-07-97
		AU 7835194 A	03-04-95
		CA 2168751 A	23-03-95
		CN 1131391 A	18-09-96
		CN 1134669 A	30-10-96
		CZ 9600722 A	16-10-96
		CZ 9600793 A	16-10-96
		EP 0719143 A	03-07-96
		EP 0719140 A	03-07-96
		FI 961213 A	14-05-96
		HU 75874 A	28-05-97
		HU 75873 A	28-05-97
		JP 9502722 T	18-03-97
		JP 9502727 T	18-03-97
		NO 961041 A	14-05-96
		NO 961052 A	14-03-96
		NZ 274346 A	24-06-97
		WO 9507694 A	23-03-95
		US 5478852 A	26-12-95
		US 5602133 A	11-02-97

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01521

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 319288 A	07-06-89	US 4798835 A	17-01-89
		AU 2647188 A	08-06-89
		CA 1313139 A	26-01-93
		DE 3875324 A	19-11-92
		IL 88513 A	12-04-94
		JP 1186883 A	26-07-89
		JP 1770963 C	30-06-93
		JP 4060582 B	28-09-92
EP 312913 A	26-04-89	DE 3735525 A	03-05-89
		AU 2394388 A	20-04-89
		ES 2032922 T	01-03-93
		JP 2091020 A	30-03-90
		JP 2539257 B	02-10-96